REMARKS

The present application has been amended to insert the Sequence Listing. Claims 1, 3 and 5-8 are pending after entry of the amendments set forth herein. Claims 2, 4 and 9-14 are canceled without prejudice. Claims 1, 3 and 6 are amended. Support for the amendments to Claim 3 is found at paragraph 22 of the specification. No new matter is added. Reconsideration is requested.

Certification Regarding Sequence Listing

I hereby certify that the enclosed Sequence Listing is being submitted under 37 CFR §§ 1.821(c) and (e) in paper and computer readable form.

As required by 37 CFR 1.821(f), I hereby state that the content of the paper and computer readable copy of the Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(c) and (e) are the same.

I hereby certify that the enclosed submission includes no new matter. The Sequence Listing was prepared with the software FASTSEQ, and conforms to the Patent Office guidelines. Applicant respectfully submits that the subject application is in adherence to 37 CFR §§ 1.821-1.825..

Claims 1-4, 6 and 7 are objected to because the claim includes subject matter of the non-elected inventions. Claims 3, 6 and 7 have been amended and are specifically drawn to analysis of the genotype of K8 at position 340. Claims 1-2 remain broader in scope, as Applicants reserve the right to petition for review of the restriction requirement.

The Office Action has required submission of a Sequence Listing. A substitute Seqlist is attached herewith, and the specification is amended to provide sequence identifiers. Applicants note the Examiner's citation of page 2 of the specification, but are not able to identify sequences required for listing. The notation of CGT→CAT does not refer to a single sequence of 6 nucleotides, rather it denotes an alteration of a single 3 nucleotide codon from one sequence to a mutated sequence. Applicants respectfully submit that the present application is in compliance with the requirements of 37 CFR 1.821 – 1.825.

Claims 1-4, 6 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office Action states that the claims do not recite a clear nexus between the preamble of the claims and the final process step.

Independent claims 1 and 3 have been amended and recite that the mutation in the specified sequence is associated with a predisposition to disease, and to clarify the intended subject matter. In view of the amendments, withdrawal of the rejection is requested.

Claims 1 and 2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants respectfully submit that the present specification meets the requirements of 35 U.S.C. 112, first paragraph.

The law regarding enablement of inventions is clear: "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."[1]

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.[2]

The instant specification teaches multiple mutations, both in keratin K8 and in K18, that are associated with liver disease, as shown in Tables 3 and 4, which mutations cover a number of different residues in these proteins. It is noted that many of these mutations have an underlying molecular logic, in that there is a destabilization of the protein, providing for a logical nexus between genetic defect and disease. For example, Table 6 shows the molecular consequences of keratin mutations:

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1 *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

2 *Ex Parte Forman.*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Table 6. Molecular Consequences of Keratin mutations

Mutations		Potential effects
K8	R340H	Destabilization
	G433S	Altering keratin phosphorylation
	R453C	Formation of a disulfide bond
	1-465(I) RDT(468)	Destabilization
K18	Δ 64-71(TGIAGGLA)	Destabilization
	E275G	Destabilization
	Q284R	Destabilization
	T294M	Interruption of ionic interaction
	T296I	Interruption of ionic interaction

The significant number of patients described in the present application with K8/K18 mutations provide several insights into keratin-associated liver diseases. For example, K8 Y53H, K8 G61C, and most prominently K8 R340H are shown to be mutation hot spots.

Applicants respectfully submit that the specification and the amended claims, coupled with the information known in the art, would enable one of skill in the art to use the invention without undue experimentation. Relevant enablement factors are discussed in detail below.

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[3]

As the court explained[4]:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art, which routinely performs such long experiments.[5]

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3 See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
4 *In re Wands* 8 USPQ 2d at 1404
5 *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

The claimed methods relate to the use of the many different polymorphisms for keratin K8 and K18 that are provided in the application. The sequence of polynucleotides is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on different samples. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay to determine the active variants, no undue experimentation is necessary.

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[6] Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."[7] As discussed above, numerous working examples have been provided.

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with the equivalent of a doctoral degree in molecular biology techniques, although Applicants believe that a much lower skill level would be sufficient to perform the claimed methods. Furthermore, such technicians are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

There may be some non-functional variants within the genus defined by the claims. However, the courts have clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained[8]:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims

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6 In re Borkowski, 164 USPQ at 645.
7 *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).
8 *In re Angstadt*, 190 USPQ at 218.

would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ...."

In sum, the amount of experimentation required to practice the methods of the invention would not be undue because a) a working example has been provided, b) guidance is given on how to test the sequences has been provided, and c) one of skill in the art would be able to perform the experiments as a matter of routine to determine the sequences.

The Office Action has stated that "it is well-recognized in the art that associations between polymorphisms and phenotypic traits are often irreproducible". Applicants submit that the present invention is based not only on association studies, but on supporting animal models. Further, the use of association studies is well-supported in guiding human health decisions. For example, the odds ratio for liver failure associated with the genetic markers of the present invention is higher than the odds ratio for the well-known association of smoking and heart disease.

The Office Action asserts that "it is highly unpredictable as to whether the results obtained in the present study can be extrapolated to other ethnic groups", however Applicants have found, as evidenced in their manuscript (abstract below) that keratin variants predispose to liver failure in multiple ethnic groups.

ABSTRACT

Background: Keratins 8 and 18 (K8/K18) provide anti-apoptotic functions upon liver injury. The cytoprotective function of keratins explains the over-representation of K8/K18 variants in patients with cirrhosis. However, K8/K18 mutation-associated susceptibility to acute liver injury, which is well-described in animal models, has not been studied in humans. **Methods:** We compared the frequency of K8/K18 variants in 344 acute liver failure (ALF) patients (49% acetaminophen-related) and two control groups [Blacks (245 subjects) and previously-analyzed Caucasians (727 subjects)]. Acetaminophen toxicity was tested in transgenic mice expressing the human-associated K8 G62C and R341H variants. **Results:** There were 45 ALF patients with significant amino-acid-altering K8/K18 variants including 23 with K8 R341H and 11 with K8 G434S, and an increased frequency of variants in Caucasian ALF patients (9.1%) versus controls (3.7%) ($p=0.01$). K8 R341H was more common in Caucasian ($p=0.01$) and G434S in black ($p=0.02$) ALF patients versus controls. Furthermore, Caucasians with K8/K18 variants were less likely to survive ALF without transplantation ($p=0.02$). K8 A333A and G434S variants associated exclusively with Blacks (23% combined frequency in Black but none in Caucasian controls; $p<0.0001$). Transgenic mice that express K8 R341H or the common variant, K8 G62C, have higher susceptibility to acetaminophen-induced ALF. K8 G434S interferes with phosphorylation of the adjacent physiologic phosphorylation site, K8 S432, and leads to increased degradation of the K8 partner, K18, during apoptosis. **Conclusions:** *KRT8/KRT18* are important susceptibility genes for ALF development. The presence of K8/K18 variants predisposes to an adverse ALF outcome, and some variants segregate with unique ethnic backgrounds.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. In view of the

above amendments and remarks, withdrawal of the rejection is requested. Applicants note that Claim 3 as presently amended is restricted to determination of a specific mutation of keratin K8 in human samples, for a predisposition to noncryptogenic liver disease.

Claims 1 and 2 have been rejected under 35 U.S.C. 102(b) as being anticipated by Ku et al (Molecular Biology of the Cell. Nov 2001. 12, Supplement 1, page 56a, abstract #303; cited in the IDS of November 17, 2005); as being anticipated by Ku et al (The New England Journal of Medicine, May 2001. 344: 1580-1587; cited in the IDS of November 17, 2005); and as being anticipated by Ku et al (Gastroenterology. published 26 March 2002. Vol. 122, Supplement 4, p A80, abstract #665; cited in the IDS of November 17, 2005).

Applicants respectfully submit that the presently claimed invention is not anticipated by the cited art. The present claims have been amended to recite the specific mutations set forth in the present application, as used in the detection of a predisposition to noncryptogenic liver disease, and thus is outside of the teachings of the cited art.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-297.

Respectfully submitted,
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Date: Dec. 1, 2008

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